REMARKS

Reconsideration of the above-identified patent application in view of the amendment above and the remarks below is respectfully requested.

No claims have been canceled or added in this paper. Claims 1, 9, 18-21 and 28 have been amended in this paper. Therefore, claims 1-28 are pending and are under active consideration.

Claims 1-28 stand rejected under 35 U.S.C. 112, second paragraph, "as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." As best understood by Applicants, the rejection appears to be predicated on the use in the claims of the alleged trademark/trade name "Scorpion."

Without acquiescing in the propriety of the subject rejection, Applicants have amended the claims so that "Scorpion" is no longer recited. Therefore, the subject rejection is moot and should be withdrawn.

Claims 1-2 and 4-28 stand rejected under 35 U.S.C. 103(a) "as being unpatentable over Eads et al. (Nucleic acids Research 2000 Vol. 28 p. 32) in view of Solinas et al. (Nucleic acids Research 2001 Vol. 29 p. e96)." In support of the rejection, the Patent Office substantially repeats its reasons of record and then states the following:

> The reply traverses the rejection. A summary of the arguments presented in the reply is provided below with a response to arguments following.
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> The reply asserts that there is an important advantage of the present invention to analyze short DNA fragments (p. 11 1st paragraph).
>
> The reply asserts that DNA from paraffin and bodily fluids is fragments and therefore easily attackable by DNAses (p. 11 2nd full paragraph). The reply asserts that DNA is further fragmented as a

result of bisulfite treatment (p. 12 1st paragraph). The reply asserts that scorpion method is well suited for the analysis of short DNA fragments (p. 12 2nd paragraph).

The reply asserts that neither Eads et al. or Solinas et al. teach or suggest such a use (p. 12 2nd paragraph). The reply asserts that one of ordinary skill in the art applying Scorpion for mutational analysis would not have been confronted to the same extent with the problem of fragmented DNA analysis that does not involve a bisulfite conversion (p. 12 2nd paragraph).

The reply asserts that additional experimental data shows that there is a quantitative determination of the methylation degree of prostate biopsies (p. 12 3rd paragraph).

These arguments have been fully reviewed but have not been found persuasive.

In response to applicant's argument that the ordinary artisan would not have recognized that the Scorpion assay method would be useful for small fragments produced by bisulfite treatment, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See Ex parte Obiaya, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

As stated in the 35 USC 103(a) the ordinary artisan would be motivated to modify the methylation method of Eads et al. to include Scorpion primers linked to probes as taught by Solinas et al., because Solinas et al. teaches the use of Scorpion primers in PCR assays allows an intermolecular probe-target interaction which results in a vary fast and reliable detection system (p. 1 2nd column 2nd paragraph). Therefore the ordinary artisan would be motivated to use Scorpion primers to detect methylation and nonmethylation sites fast and reliably. Therefore the ordinary artisan would be motivated to use Scorpion primers because they allow for a very fast and reliable detection system, the fact that the Scorpion primers would detect small fragments more reliably is another advantage which would flow naturally from following the suggestion of the prior art.

It is noted that the reply has brought in evidence of the usefulness of the method. It is noted that evidence must be brought in

> the form of a declaration. However, the results presented have been reviewed in order to provide compact prosecution. It appears that the results merely show that the claimed method would work on a particular fragment. However, these results do not show that the method would not be obvious in view of the combination of art presented above or that the method produces unexpected results. As such the results presented in the reply do not overcome the 35 USC 103(a) on the record.

Applicants respectfully traverse the subject rejection. As explained below, it would not have been obvious for a person of ordinary skill in the art to combine the applied references in such a way as to arrive at the claimed invention.

First, based on the method described by Eads et al., there would have been no reason to attempt to modify the MethyLight method by including the Scorpion primers linked to probes as taught by Solinas et al. According to Eads et al., the MethyLight methylation assay has the advantages of being highly specific, sensitive and reproducible, and further being compatible with very small amounts of template DNA and allowing to rapidly analyzing many samples at multiple gene loci (page ii, first column, second paragraph). Based on a reading the aforementioned passage, a person of ordinary skill in the art would not have been motivated to further developing methylation assays to arrive at some advantages mentioned by the instant application, i.e., inter alia an effective, rapid, sensitive and very specific methylation analysis (page 3, last paragraph of the description). This is further evident since the benefits of the Scorpion primers are taught by Solinas et al. are basically similar to those of the present method, namely, providing a "fast and reliable detection system" (page 1, first column, last paragraph) for allelic discrimination which gives "a lower background than Taqman™ probes," i.e., which works with a higher specificity as methods known in the art (page 5, second column, second paragraph).

However, it was not obvious to attempt to modify a method in order to arrive at the additional advantages of detecting the methylation status of short fragments of sample DNA as they occur within bisulfite treated DNA and DNA from tissue samples or bodily fluids, claimed by the instant application (claim 1, step e)). The motivation to modify the MethyLight assay by including the Scorpion primers rather was to optimize MethyLight for the methylation analysis of short fragments of sample DNA by shortening the probe sequence without decreasing the specificity of the assay (see page 6, lines 6-11 of WO 2005/024056). There was no incentive for a person of ordinary skill in the art, reading the cited references, to develop an assay with the same advantages as disclosed in both cited references. The present method claims the surprising effect of combining the MethyLight assay with the Scorpion primers to arrive at detecting short sample DNA fragments. This is highly desirable since the bisulfite conversion, which is part of the MethyLight approach, results in extensively fragmented DNA. In contrast to the Patent Office's view that this advantage would flow naturally from following the suggestion of the prior art, the advantage of the scorpion method to be well-suited for the analysis of short DNA fragments in bodily fluids and bisulfite-converted sample DNA represents not only another advantage that has been surprisingly realized by Applicants in retrospect. In view of the fact that neither Eads nor Solinas teaches or suggests the application of their methods for the analysis of short DNA fragments, the Patent Office should not succumb to hindsight claims of obviousness.

Second, if there existed only a finite number of identified predictable solutions to arrive at the above-mentioned advantages, then the invention could be argued to be obvious. However, the advantages of the present invention are achieved by the application of Scorpion primers in

methylation analysis. This approach was not obvious since there are numerous possible choices of primers that a person of ordinary skill in the art would use for DNA methylation analysis. Eads et al., for example, describes five sets of PCR primers and probes, designed specifically for bisulfite-converted DNA (page ii, second column, first paragraph). The used primers differ regarding their function and their sequence. Moreover, Eads et al. by no means mentions which of the parameters of their method are critical to arrive at the mentioned advantages, i.e., in which way alternative primers like the Scorpion primers could assert the same or even an improved performance in terms of sensitivity or reliability. Finally, since Solinas et al. does not mention any other advantage besides that the Scorpions system represents a "very fast and reliable detection system" (page 1, second column, second paragraph), a person of ordinary skill in the art would not have had any motivation to choose the Scorpion primers of all possible primers in order to modify the MethyLight assay. By the time the invention was made, the Scorpion primers did not offer any advantage over the MethyLight technology.

Third, the MethyLight technology was described in Eads et al. in 2000, whereas the application with the earliest priority claimed by the method was filed on May 14, 1999, and issued in 2001 (U.S. Patent No. 6,331,393). The Scorpion primers were described in Solinas et al. in 2001; however, the first disclosure of "a tailed nucleic acid primer comprising, in 5' to 3' order, a template binding region and a tail comprising a linker and a target binding region" (U.S. Patent No. 6,326,145, Claim 1, step (a)) claims priority of June 13, 1998. Consequently, both the MethyLight method and the Scorpion primers had been filed by May 14, 1999. However, the foreign priority claimed by the instant application is August 15, 2003. Accordingly, by the time the present invention was filed, the

relevant teachings of both cited documents had been publicly available already for over 4 years. With regard to the speed of development within the field of biotechnology, this is to be regarded as quite a long period of time. Therefore, if the combination of both prior art documents would have been obvious to a person of ordinary skill in the art, competitors would have come up with the present invention during this time, i.e., before the present invention was filed. The fact that this was not the case and that even the inventors did not consider the use of a scorpion primer in connection with the MethyLight assay indicates that, to a person of ordinary skill in the art, it was not obvious to combine both methods in order to develop the present invention.

Fourth, the method of the present invention has been licensed to a third party. This indicates that the present combination of the MethyLight assay with the Scorpion primers is not obvious. Moreover, the existing licensing agreement indicates the commercial success of the method, as well as its suitability to solve long-standing needs within the field of methylation analysis. In summary, the licensing of the present invention is a strong indicator of nonobviousness. Evidence of license agreements and reluctance of others to arrive at the claimed invention as explained above is relevant to the non-obviousness of the claims of the present application because competitors would have been commercially motivated to make the invention before Applicants. The presence of a license agreement supports the finding that the claimed invention is superior to existing methylation assays and is, therefore, a non-obvious advance over the prior art.

Accordingly, for at least the above reasons, the subject rejection should be withdrawn.

Claim 3 stands rejected under 35 U.S.C. 103(a) "as being unpatentable over Eads et al. (Nucleic acids Research 2000 Vol. 28 p. e32) in view of Solinas et al. (Nucleic acids Research 2001

Vol. 29 p. e96) as applied to Claims 1-2 and 4-28 and in further view of Berlin et al. (US Patent Application Publication 2006/0183128 August 17, 2006)."

Applicants respectfully traverse the subject rejection. Claim 3 depends from claim 1. Claim 1 is patentable over Eads et al. in view of Solinas et al. for at least the reasons given above. Berlin et al. fails to cure all of the deficiencies of Eads et al. and Solinas et al. with respect to claim 1. Therefore, based at least on its dependency from claim 1, claim 3 is patentable over the applied combination of Eads et al., Solinas et al. and Berlin et al.

Accordingly, for at least the above reasons, the subject rejection should be withdrawn.

Claims 1-28 stand provisionally rejected "on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1-4, 15-16, 18 of copending Application No. 11716207 in view of Solinas et al. (Nucleic acids Research 2001 Vol. 29 p. e96)."

Applicants respectfully traverse the subject rejection. A rejection for obviousness-type double patenting requires a two-step analysis. First, one must determine whether the later claims "encompass" subject matter previously claimed. Second, one must determine if the later claims are patentably distinct from the earlier claims.

The Patent Office is apparently taking the position that USSN 11/716,207 is drawn to the same method steps as those of the present application. However, the '207 application does not claim that the primer is joined with a probe via a linker.

Applicants respectfully submit that the Patent Office has overlooked the claimed subject matter of the aforementioned applications. In particular, the Patent Office has misapprehended the subject matter of the '207 application by stating that it would have been obvious to a person of

ordinary skill in the art to modify the methylation method of the '207 application. This is because claim 1 of the '207 application discloses a method of identifying at least one biological sample in the field of methylation analysis, i.e., it relates to detecting sample interchange and/or sample cross-contamination for methylation analysis (see page 3, fourth paragraph, of the '207 application). Claim 1 of the '207 application by no means relates to the detection of cytosine methylation in DNA as claimed in the instant application. Therefore, the claimed subject matter of the instant application does not encompass subject matter of claim 1 of the '207 application.

Therefore, in addition to the previous arguments, inter alia, mentioned against the obviousness rejection in light of Solinas et al. and Eads et al. that there was no motivation for a person of ordinary skill in the art to use the scorpion primer in detecting cytosine methylations in DNA, the claimed subject matter of the '207 application, in particular claims 1-4, 15-16, and 18 differs from the claimed invention, and the claims of the present application are not coextensive in scope from the claims of the '207 application. Consequently, the subject nonstatutory double rejection is improper.

Accordingly, for at least the above reasons, the subject rejection should be withdrawn.

Claims 1-2 and 4-28 stand provisionally rejected "on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1-2, 11, 14, 18-19 and 27 of copending Application No. 10482433 in view of Solinas et al. (Nucleic acids Research 2001 Vol. 29 p. e96)."

Applicants respectfully traverse the subject rejection. The Patent Office states that the '433 application is drawn to the same method step as the claimed invention; however, the '433 application does not claim that the primer is joined with a probe via a linker.

Claims 1-2 and 27 of the '433 application relate to the detection of the methylation state of a pre-defined segment of a genomic DNA sample by, inter alia, target-specifically amplifying and investigating the difference between the molecular weights of the two individual strands of the amplified pre-defined fragments. The technical principle of this method is the fact that the conversion of unmethylated cytosine to thymine results in an increase of the molecular weight by 15 Da per converted cytosine, which can be measured, e.g., by means of mass spectrometry.

However, claims 1-2 and 27 of the '433 application differ from the instant application in that they claim detection of the methylation state of a pre-defined segment of a genomic DNA sample, i.e., **the sequence of the sample DNA to be analyzed which is chemically treated in a first step is known**. However, in claim 1 of the instant application, the DNA sample obtained from tissue samples or bodily fluids are not pre-defined segment in a first step.

Further, claim 1 of the '433 application claims target-specifically amplifying of the pre-defined segment of a genomic DNA sample, which means that the primers that are used to target-specifically amplify a pre-defined segment of a genomic DNA sample are specific for a part of the chemically treated segment of the genomic DNA itself, which is also already present in the genomic DNA sample. In other words, the primers are specifically hybridizing to a sequence representing a part of the chemically modified sequence of the segment, which is already present in the DNA sample analyzed. In addition, claim 1 of the '433 application claims investigating the difference between the molecular weights of the two individual strands of the amplified pre-defined fragments.

In view of the above-mentioned differences and the use of scorpion primer that exists between claims of the '433 application and the instant application, the present rejection is improper.

Accordingly, for at least the above reasons, the subject rejection should be withdrawn.

In response to the above, Applicants respectfully request that the subject provisional double patenting rejection be held in abeyance at least until the Patent Office has allowed one of the two patent applications at issue.

In conclusion, it is respectfully submitted that the present application is now in condition for allowance. Prompt and favorable action is earnestly solicited.

If there are any fees due in connection with the filing of this paper that are not accounted for, the Examiner is authorized to charge the fees to our Deposit Account No. 11-1755. If a fee is

required for an extension of time under 37 C.F.R. 1.136 that is not accounted for already, such an extension of time is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on December 10, 2009

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